It is interesting to note, from the table presented, that both betanaphthol and balsam Peru in concentrations much less than employed in this formula are among the most active scabicidal drugs tested. In this case the experimental findings confirm our clinical experience of the remarkable efficacy of this particular combination of substances. By further experimentation along the lines suggested by the authors of this paper, however, it is entirely reasonable to assume that a more efficacious and less irritating remedy will be found.

URINARY TRACT INFECTION WITH "CLEAR URINE" *

By JAMES R. DILLON, M.D.
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DISCUSSION *by Robert V. Day, M.D., Los Angeles; F. S. Dillingham, M.D., Los Angeles; Charles P. Mathé, M.D., San Francisco.*

IT is surprising how many times medical men fail to recognize urinary tract infection in fairly typical clinical pictures because there is no pus in the urine, which may be macroscopically clear. This occurs particularly in both the acute and chronic coccal kidney infections, where the microscopic examination of the urine may show only a few red cells, few or no pus cells, and by the ordinary routine bacteriologic examination, few or no cocci. The urine in acute bacillary infections is practically always cloudy macroscopically, but microscopically may show only a few or no pus cells; the cloudiness being due to bacilli only, which is often considered a contamination, and the patient is treated as a "flu" condition, or possibly extensive examinations are carried out to differentiate typhoid, malaria, and other infective conditions, with a neglect of the urinary tract. Chronic bacillary infections also frequently occur with macroscopically clear urines which reveal no pus microscopically, and few or no bacilli are reported by the bacteriologist. This report is presented for the consideration of the diagnosis and etiology of various clinical pictures rather than treatment, it being evident from the histories of patients of repeated urologic examinations that diagnosis in this type of case is frequently missed by the urologists as well as internists. Nor does it include the cortical renal lesions or the so-called carbuncle of the kidney; nor the perirenal abscess types.

About fourteen years ago my attention was first attracted to the possibility that sometimes bacteria appear in the urine in "showers" during the acute stage, which may last only a few hours, and with three or four voidings the urine may be entirely clear of pus and with relatively few or no bacteria present.

REPORT OF CASE

CASE 1.—A medical woman, actively practicing with her husband, also a medical graduate, complained of a pain in her right side, ran a low-grade temperature, rarely reaching 100 degrees, except during the acute attacks. The pain and tenderness seemed to be definitely in her right kidney, but cystoscopic examination and pyelograms by three different urologists, over a period of one year, showed normal pyelograms and negative urine reports from the bacteriological laboratories. One of the urologists passed four catheters up the right ureter, three of them stopping just below the pelvic brim at the site of an apparent ureteral stone shown in the x-ray, but at surgery this proved to be a phlebolith, and she continued to have her attacks. She resided about one hundred miles from San Francisco, and would have an attack (at intervals from two to six weeks) of rise in temperature, increased pain and tenderness, burning and frequency of urination. Samples of the urine during this onset would be loaded with pus and colon bacilli. She would start by automobile with the onset of the attack, and by the time she reached my office, in about three and one-half hours, voiding three or four times on the way, a catheterized specimen would be crystal-clear and the bacteriological laboratory report would be negative. On the eighth trip pus and colon bacilli were found in a catheterized specimen, and an immediate cystoscopic examination and collection of segregated urines showed the left kidney sterile and the infection entirely in the right kidney. Her tonsils had been removed and all possible foci checked by myself, as well as the two preceding urologists. Doctor Rigdon had been in consultation several times, and we finally decided it was a blind abscess in the renal cortex, which at times discharged into the renal pelvis. At operation we thoroughly exposed the kidney, pelvis, upper end of the ureter pedicle, and finally did a nephrotomy, exposing the pelvis from pole to pole. Cultures taken of the urine in the pelvis, on opening it, and sections of renal parenchyma were negative for signs of infection or pathology. She made an uneventful recovery, but I carried a guilty conscience until I met her several years afterward and she thanked me again, stating she had never had another attack after the operation.

OTHER TYPES

Cases of urethritis in males with coccal infections, showing a very slight purulent or mucopurulent discharge, or merely a glueing of the meatus in the morning, are sometimes treated over an indefinite period as a chronic gonorrhea or gleet. The two- or three-glass test may show all crystal-clear, with the first glass containing a few shreds, or possibly presenting a faint haze. The bacteriologic report of the second or third glass, as ordinarily done, will generally be negative, few or no pus cells, few or no red cells, or a few described bacteria, either coccal or bacilli, and if there is a scanty growth on the cultures, the opinion will be expressed "probably contamination," and the patient goes on being treated as an urethritis. I have had bacteriologists make the statement to me, when their cultures are slightly positive, that they were probably contaminations because the smears of the sediment did not show any pus. Men will also frequently appear complaining of frequency of urination, with slight bladder-neck sensitiveness or consciousness, revealing a macroscopically clear urine with a negative pus and bacteriologic report, and if the patient has no chronic prostatitis, he is lucky if he does not have one immediately made by repeated massaging. Or, if he is fortunate in having his prostate acquitted at the first trial, he may be retried and condemned as a neurotic. These bladder-neck irritabilities occur in both men and women, who suffer for indefinite periods because a diagnosis and cause is not ascertained. There are other clinical pictures appearing as a septic condition, with no symptoms referable to the urinary tract, and presenting macroscopically clear urine.

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BACTERIOLOGIC LABORATORY: ITS PLACE

In recent years I have come to depend less on the professional bacteriologic laboratories for my urine examinations, especially in the case of the ambulatory patient who comes to my office. Practically all of such reports are based on the smears and cultures made from the sediment of one centrifuge tube of urine. If the infective products are sufficiently diluted in the urine that it is macroscopically clear, those products will be very likely missed in the study of the centrifuged sediment of one tube of urine. I have trained my office nurse to concentrate the sediment of the entire collection of catheterized urine in the female and the third glass of voided urine in the male until she can plainly see a film of sediment in the bottom of the centrifuge tube. This is done by filling the centrifuge tube, vigorously centrifuging it and pouring off the supernatant urine and refilling it. This is repeated until the sediment of the entire specimen, amounting to six or eight ounces, as a rule, is concentrated in one tube. The supernatant urine from the last filling is poured off quickly, holding the tube in an inverted position until the smear is made from the scrapings from the bottom of the tube. The smears are fixed and stained with 1 per cent methylene blue, and for most cases we are only interested at this time in whether infection is present and whether it is coccal or bacillary. If present, it is then incumbent upon us to not only make a further urologic study by intravenous urography, cystoscopy, and possibly retrograde pyelograms, but also to determine the etiologic factor and its removal. Women frequently will be apparently cured of an urinary-tract infection, and the urine may be reported free of pus and bacteria, but they may continue to complain of bladder irritability, frequency, and urgency. Cystoscopic examination will reveal a normal-appearing bladder, but the distal side of the vesical orifice will show an inflammatory condition of the urethral mucosa, or, if of long standing, may show a fringe of polypi.

RÔLE OF ALVEOLAR INFECTIONS

My personal opinion is that infection and absorption of the alveolar process is the source of most of our upper urinary tract infections. I try to avoid the term "infected teeth," which is a dental problem, but an infected alveolar process, signifying really an osteomyelitis, is a medical and surgical problem, and we must seek those dentists who recognize this fact to coöperate with us in the proper surgical treatment. We must train ourselves in the study of x-ray dentures, insist on inspecting them ourselves, and follow up with further x-ray studies in three to six months' intervals to see that pathologic conditions in the alveolar process have really cleared up, before we are qualified to challenge the statements of those who are experienced in this study and believe such foci to be causative factors. Our search for foci should not end here, but all possible primary areas of infection, such as tonsils, sinuses, middle ear, skin, bowel, rectal and genital, etc., should be eliminated. Also, there is evidence that the primary infection of the kidneys may be very transient, clearing up spontaneously where the ureteral drainage is adequate; but it may then continue indefinitely as a trigonitis and urethritis, and serve as a focus for blood-stream or lymph-stream dissemination, or direct ascent by the ureter, and so produce recurring attacks of pyelonephritis after the primary focus has been removed.

The following are a few case histories illustrating the various clinical pictures of "clear urine" with urinary tract infection:

REPORT OF CASES

CASE 2.—A husky Danish ambulatory longshoreman complained of frequency of urination with occasional urgency. Examination negative, except for the concentrated sediment of a "clear urine" showing a streptococcus, later confirmed by the bacteriologist as Streptococcus viridans. He would be temporarily relieved by bladder irrigations and urinary antiseptics, and was finally completely cleared up after several recurrences by getting a marked pyorrhea properly treated.

* * *

CASE 3.—A ten-year-old school boy (one of four in the last year) complained of urgency, frequency, and feeling tired. Urine was clear, but showed trace of albumen, occasional casts and red cells, and the concentrated sediment showed a streptococcus, also confirmed by the bacteriologist. Cystoscopic examination and pyelograms were negative. He was put on urinary antiseptics, and a week later complained of a "gum boil." With the removal of a deciduous tooth, his urinary tract spontaneously cleared of albumen, blood, and streptococci.

* * *

CASE 4. — A fifteen-year-old girl (the daughter of a medical man), strong, athletic, ambitious, but all her life had been subject to attacks of chills, fever, and prostration, every two or three months. She had been examined by internists, until one discovered she had a "floating right kidney" and suggested a cystoscopic examination, which disclosed a catheterized urine free of pus, but hazy with colon bacilli coming from the dilated functionless left half of a "horseshoe kidney." She was cured by nephrectomy.

* * *

CASE 5.—A Jewish woman, age sixty-five, complained of frequency and urgency; also had a great liking for "sprees" on barbital drugs. She had been pronounced cured of a urinary-tract infection, but continued to suffer bladder symptoms for many months and was treated more as a mental case. Examination of the concentrated sediment of a catheterized specimen of "clear urine" showed a trace of pus and a fair smear of colon bacilli. Cystoscopic examination showed normal kidneys, but a fringe of polypi on the urethral edge of the bladder neck. Removal of all her remaining teeth, about ten, around which there was marked pyorrhea, fulguration of the polypi, followed by a few urethral dilatations and bladder irrigations with urinary antiseptics, cleared up the urinary tract entirely.

* * *

CASE 6.—A young Italian, age twenty-one, presented an acute septic condition, temperature 104 degrees, with pain in the right side, diagnosed appendicitis. A normal appendix was removed, but the septic condition continued for four months, with symptoms apparently localizing in the right kidney. Absolutely clear urine persisted throughout the entire course, except on one occasion, when a Streptococcus hemolyticus was obtained. A diagnosis was made by the urologist, from the pyelogram and intravenous urogram, of a Streptococcus cellulitis around the middle calyx of the right kidney. Through lack of coöperation, an x-ray denture was not obtained until he developed a toothache at the end of the four months of septic temperature, disclosing an abscess on the root of another tooth, on the extraction of which his temperature dropped to normal within forty-eight hours, where it has since remained.

CASE 7.—A woman, twenty-nine years old, complained of urgency and frequency shortly after the onset of a crop of boils on the buttocks. The concentrated sediment of a "clear urine" showed a good smear of staphylococci with no pus. It cleared up with bladder irrigations and urinary antiseptics along with the disappearance of the boils. Three years later she again had the same bladder symptoms, with staphylococci in a "clear urine." This time she complained of pain and soreness in the rectum, and on the removal of an anal fissure and a rectal cryptitis by a proctologist, her attending nurse volunteered the statement that her bladder capacity had increased from five to twelve ounces within forty-eight hours, and along with the urinary antiseptics and bladder irrigations her urine is again sterile.

CONCLUSIONS

1. Foci of infection play an important part in the causation of urinary tract infections.

2. In vague septic conditions more attention must be paid the urinary tract as a possible location of infection, in spite of the negative clinical examination of the urine.

3. Dentists should be taught to recognize more of the medical and surgical aspects of an infected alveolar process.

4. Before condemning patients with bladder symptoms with "clear urine" as neurotics, we should send larger quantities of bladder urine to the bacteriologist with the request that the examination be made on the concentrated sediment of the entire specimen.

5. Children should be watched more closely during the tooth-cutting age, and attention given to dental care and hygiene. Also, during the septic reactions, the urinary tract should not be forgotten, and more exacting examinations should be made for the presence of bacteria in the "clear urine."

490 Post Street.

DISCUSSION

ROBERT V. DAY, M. D. (1930 Wilshire Boulevard, Los Angeles). — Doctor Dillon has brought to our attention some particular phases of urinary infections which are often overlooked.

I should like to emphasize his meaning by using the term "seemingly clear," or "nearly clear urine." In such cases the specimen is apt to be of low specific gravity and, hence, exceedingly diluted. By greatly restricting the intake of fluids for twelve hours, one can frequently obtain a urine of a specific gravity of 1.020 or so, in which case the amount of pus is usually sufficient to show cloudiness to the naked eye except in those cases where only a few bacteria are present in the urine. These cases are often very baffling until observed over a considerable period of time.

Our first duty is to determine the presence or absence of infection by repeated urine examinations and, if present, to identify the organism responsible for the infection. For this purpose, both stained smears (preferably a Gram stain) and cultures are invaluable.

If urinary infection is demonstrated, then one may proceed methodically to discover each and every anatomical focus of infection by cystoscopic and other recognized urologic procedures.

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F. S. DILLINGHAM, M. D. (1016 Story Building, Los Angeles).—In the past a great deal of thought has been given to pyelonephritis, and today Doctor Dillon has called our attention to a phase which, kept in mind, may save a long course of illness by promptly leading to the correct diagnosis. In 1916 Crabtree and others noted that, early in an attack of pyelonephritis, there may be a great drop in phthalein output due to a cloudy swelling, probably involving the tubular portion which is short-lived, and which goes on to complete recovery, as shown by the return of kidney function and even on microscopic sections.

It may be our misfortune to see these patients only in the intervals as in the case of the doctor's wife, who was only three and a half hours away, and not until the eighth examination were bacteria found. Is it possible that in Doctor Dillon's extensive exploration of this patient's kidney some minor kink was relieved, or nerves or lymphatics cut that resulted in freedom from attacks?

When the specimen is macroscopically clear in a suspected patient, Doctor Dillon's suggestion of concentrating the smear to be examined is as important as running the centrifuge at high speed for a longer interval when searching for tubercle bacilli. Also, the freshness of the urine specimen is of importance, as many come with specimens twenty-four to forty-eight hours old, in questionable containers, that are macroscopically cloudy, and yet after proper cleansing a fresh specimen is found to be free of pus, blood or bacteria.

In 1917, E. H. Stephens stated that simple bacilluria may exist without cells in the urine. Livermore found stasis to be the chief cause of renal infection; as there may be foci, but without stasis, there will be no infection unless there is an overwhelming amount of bacteria. Rovsing found that infection could not be caused without retention or trauma.

In 1916, Eisendrath and Kahn found that infection travels from the bladder to the kidney and perinephritic tissue by way of the lymphatics in the wall of the ureter and not along its mucous membrane. The lymphatic capillaries of the periureteral sheath play a most important part in ascending infection. Franke found that the lymphatics of the ascending colon communicate with those of the right kidney. Cystitis and renal infections following gynecologic operations take place by way of the lymphatics. With care not to cause trauma, emulsions of bacteria were injected into the bladder; (Bacillus coli, Staphylococcus aureus, Proteus vulgaris, gonorrheal pus). Inflammatory infiltrations followed the course of the lymphatics, beginning in the submucous layer of the bladder, especially around the smaller blood vessels in this layer, and this holds true for the lower ureter. Higher along the ureter, in addition to the submucous infiltration, there is infiltration around and in the walls of the blood vessels of the periureteral sheath. Later the other coats become invaded from without inward, the mucosa remaining intact until the infection is well advanced. In the kidney pelvis, the infiltration is seen first in the subpelvic areolar tissue, and again around the blood vessels, the overlying mucous membrane remaining intact. In the kidney the infiltration is seen first around the renal vessels which pass into the parenchyma. In the cortex, between the tubules and around the glomeruli, and as the infection advances, the medulla is invaded in the same intertubular manner, and finally infiltration breaks into the lumen of the tubule. The infiltration follows closely the lymphatics which allow of communication between the cortex and those penetrating the true capsule which, in turn, communicate with the perinephritic tissue. They are convinced, as Bauereisen and others assert, that there is free communication between the lymphatics of the bladder and of the ureter, and that the lymph current is upward. The connecting link between the lower ureter and those within the kidney is along the lymphatics of the subpelvic areolar tissue which surrounds the blood vessels as they enter the kidney tissue. In none of the laboratory animals were the bacilli recovered from the heart's blood. Lymphatics of the lower genito-urinary tract, David MacKensie and A. B. Wallace (*Journal of Urology*) conclude: "Dye injected in small quantities in rabbits to different areas of the bladder wall, different levels of the ureteral wall and cervix, is absorbed and passes to the common iliac group of glands, either directly or through interposed smaller nodes, then upward toward the thoracic duct, and the implication from one series was that the dye passes to the blood stream and to the kidney."

Examine neurotics with special care. The term usually covers the fact that a correct diagnosis has not been made, not only in the strong longshoreman or ambitious young person types, but also in weak nervous patients suffering from chronic absorption from undiagnosed foci as have been mentioned, and stasis in the intestinal as well as the urinary tract. We cannot always get a perfect history, as one woman whose symptoms were unquestionably pyelonephritis with a severe cystitis, but whose upper urinary

tract on repeated examination was found negative. Later it was brought out that a bilateral pyosalpingectomy had been performed, and due to the resultant adhesions there was direct infection of the bladder, causing the severe cystic symptoms.

Chronic seminal vesiculitis has been another source not mentioned by the author, and has caused acute attacks so severe that more than one patient has had an emergency appendectomy performed. One of our own patients, a boy of nineteen (with no symptoms referred to the kidney, ureter or bladder), complained of an acute, mild, non-specific urethritis, which would clear up with a few days' treatment, only to recur. After a month or so he voided a small ureteral calculus, when all of his symptoms were relieved. This emphasizes the necessity of a careful history and a thorough urologic study, even in those patients in which the causes may seem very simple. Red blood cells found in the urine and not accounted for should call for an examination, including intravenous urography and, if warranted, followed by a retrograde x-ray study.

In 1927 Eisendrath made a plea for the early use of the indwelling catheter, but each patient must be handled individually, because there are some acute cases in which lavage and catheter drainage aggravate the condition; and yet the same measures during another attack may act like a charm. (Hooe left a catheter in one kidney eight days and in the opposite kidney fourteen days, with no untoward results.)

Modern treatment of pyelonephritis should include the stimulation of the endocrines that have to do with infections.

Doctor Dillon has called our attention to a condition which we may meet clinically daily, and yet about which very little has been written or said.

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CHARLES P. MATHÉ, M. D. (450 Sutter Street, San Francisco).—Doctor Dillon has presented a paper in which he stresses the point that many infections of the urinary tract are overlooked because of inadequate examination of the urine. In cases in which pyelonephritis is suspected, and in which the urine is found to be clear, repeated examinations of catheterized specimens should be made because pus and bacteria might occur in showers. However, if one takes the care to make these repeated examinations he will usually encounter pus and the infecting organism. Occasionally pus and organisms fail to find their way into the bladder because of some obstructive lesion in the ureter such as a stricture or edema. In these a complete cystoscopic examination is necessary to establish a diagnosis.

When one encounters polypi on the neck of the bladder and in the posterior urethra, one should look for infection in the prostate gland and in the kidneys. These are often secondary to kidney infections, and this phenomena is often observed in the female.

The rôle of foci of infection in the production of chronic pyelonephritis has long been recognized, but not sufficiently emphasized. Years ago Rosenow, and Bumpus and Meisser demonstrated that the green-producing streptococci, originating in foci such as teeth and tonsils, have a specific predilection for the kidneys. In all cases of chronic infection, abscessed and pulpless teeth, and infected tonsils should be removed. Unfortunately, in many cases these are removed too late, when irreparable damage to the kidneys had already taken place. We have observed that, following removal of these primary foci, a severe general reaction may follow which might be accompanied by an exacerbation of pyelonephritis. This phenomena may be considered as positive evidence of the original infective focus. Modern treatment of chronic pyelonephritis should consist of systematic eradication of other possible foci, as well as infections of the skin, prostate, seminal vesicles, sinus, ear, etc. Chronic constipation and stasis in the upper and lower urinary tract should also be corrected, as these play an important rôle in the production of chronic pyelonephritis.

I recall a patient possessing a huge pyohydronephrosis presenting chronic pyuria which had been treated for chronic prostatitis for two years by a competent urologist. Because of pain in the upper abdomen, a surgeon diagnosed chronic colitis; however, on encountering a mass in the right upper abdomen, he suspected a kidney lesion and referred him to me for examination. A complete urologic study revealed a huge infected hydronephrosis secondary to an aberrant vessel, and nephrectomy cured the patient of his pyuria. I observed a similar patient presenting calculus pynephrosis who had been treated for chronic prostatitis in one of our clinics for seven years. These experiences should emphasize the importance of making a complete urologic investigation in all cases presenting chronic pyuria.

The internist and general surgeon often confuse pyelonephritis with influenza, abdominal lesions such as appendicitis salpingitis, gall-bladder disease, gastro-intestinal lesions, etc. As Doctor Dillon has so well pointed out, the distinguishing feature in its differentiation lies in painstaking, repeated urine analyses, including centrifugalization of the urine over a long period of time, and making careful cultures.

THE LURE OF MEDICAL HISTORY†

THE HUNTERS IN EMBRYOLOGY*

By A. W. MEYER, M.D.
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II**

IN addition to many fine representations of the pregnant uterus, this costly volume of William Hunter's contains drawings of dissections of the latter, and representations of the ovaries and of placentæ injected with colored wax from the uterine and umbilical vessels. Although it was the dissection and study of a doubly injected uterus, with the injected fetus *in loco*, that convinced John of the independence of the maternal and fetal circulations, the relationship of these circulations is left without comment in William's famous treatise. It is true that William referred to "RR" as "Veins emerging from the substance of the placenta and broken through at its surface, where they were passing into the womb" in connection with Plate 19, and that he said in connection with Figure II, Plate 24: "Most of the blue wax, which was first injected by the veins of the womb, was driven on towards the internal surface; and the red wax, which was afterwards injected by the arteries, was lodged principally in the outer parts; but the two colours were, more or less, blended through the whole." In one of the legends accompanying Plate 5, he spoke of "ee" as "injected veins, of a flattened figure with numerous anastomoses, passing from the womb to the placenta in a very slanting direction." "LL" of Figure 1 of Plate 24 is of "The placenta, adhering to the womb. None of the wax, injected into the vessels of the womb, had passed into the branches of those vessels which compose the navel-string; . . . but the cells, or interstices in the spungy part of the placenta, were universally loaded with wax, either the blue, which was injected into the veins of the womb, or the red, which was thrown into the arteries." In connec-

†A Twenty-Five Years Ago column, made up of excerpts from the official journal of the California Medical Association of twenty-five years ago, is printed in each issue of CALIFORNIA AND WESTERN MEDICINE. The column is one of the regular features of the Miscellany department, and its page number will be found on the front cover.

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